



DEPARTMENT OF THE AIR FORCE
AIR FORCE RESEARCH LABORATORY
WRIGHT-PATTERSON AIR FORCE BASE OHIO 45433

7 January 2002

MEMORANDUM FOR US EPA

NCEA (MD-52)
RTP, NC 27711
ATTN: ANNIE M. JARABEK

FROM: Kyung O. Yu
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SUBJECT: Consultative Letter, AFRL-HE-WP-CL-2002-0002, Intravenous kinetics of radiolabeled iodide and perchlorate in tissues of pregnant and lactating Sprague Dawley female rats dosed with perchlorate and/or carrier free ^{125}I .

1. This consultative letter presents additional GD20 dam and fetus, and PND10 lactating dam and nursing neonate data that were not available for publication in the consultative letter (AFRL-HEST-WP-CL-2000-0038; Tissue Distribution and Inhibition of Iodide Uptake in the Thyroid by Perchlorate with Corresponding Hormonal Changes in Pregnant and Lactating Rats (drinking water study)) submitted in June 2000. These data have been used in development of physiologically based pharmacokinetic models for pregnant and lactating rats (AFRL-HE-WP-CL-2001-0006 and AFRL-HE-WP-CL-2001-0007).

2. Detailed methods for ^{125}I and perchlorate analysis were reported in AFRL-HE-WP-CL-2000-0038.

a. Iodide kinetics of GD20 dams and fetuses: GD20 pregnant Sprague-Dawley dams were dosed with carrier free ^{125}I (average dose = 2.19 ng/kg) via tail vein injection and sacrificed by CO_2 asphyxiation at 0.5, 2, 4 and 8 h post-dosing. Maternal thyroid, serum, gastric contents, placenta, mammary gland and skin plus fetal serum, gastric tract and skin were collected. Levels of ^{125}I in tissues were analyzed and reported in Table 1.

b. Perchlorate kinetics of GD20 dams and fetuses: A group of GD20 pregnant Sprague-Dawley dams were dosed with 0.1 mg/kg perchlorate and sacrificed at 0.5, 1, 2, 4, 8, 12, 24 and 48 h post-dosing to harvest maternal thyroid and serum, mammary gland, placenta, skin and gastric contents as well as fetal serum, skin and gastric tract. Perchlorate levels in each tissue were determined and are reported in Table 2.

c. Inhibition kinetics of GD20 dams: GD20 pregnant Sprague-Dawley rats were dosed with perchlorate (1 mg/kg) and then carrier free ^{125}I was injected via the tail vein. Controls received physiological saline. Dams were sacrificed at 0.5, 1, 2, 4, 8, 12 and 24 h post-dosing of iodide (2.5, 3, 4, 6, 10, 14 and 26 h post-dosing of perchlorate) to collect maternal thyroid and serum and fetal serum (Tables 3 and 4).

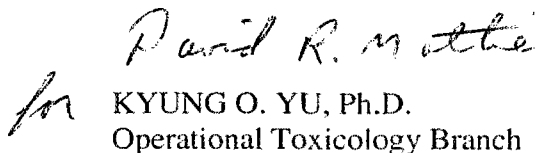
d. Inhibition kinetics of PND10 dams: PND10 lactating dams were intravenously injected with 1 mg/kg perchlorate (controls received physiological saline) and injected with carrier free ^{125}I 2 h post-dosing of perchlorate. Maternal thyroid, serum gastric contents, gastric tract, mammary gland and skin in addition to male and female neonate serum, gastric contents, gastric tract and skin were collected at 0.5, 1, 2, 4, 8 and 24 h post-dosing of ^{125}I (2.5, 3, 4, 6, 10 and 26 h post-dosing of perchlorate). ^{125}I levels were determined and reported in Table 5.

e. Perchlorate kinetics of PND10 dams: PND10 dams were dosed with 0.1 mg/kg perchlorate via tail vein injection and sacrificed at 0.5, 1, 2, 4, 8 and 12 h post-dosing to study the kinetic behavior of perchlorate in PND10 dams and neonates. Results are shown in Table 6.

3. Percent inhibition of thyroidal uptake of iodide in GD20 dams for the period of 24 hours after dosing with 1 mg/kg perchlorate was 68 to 87%. ^{125}I levels in GD20 maternal thyroids were the highest followed by gastric contents and then maternal serum. ^{125}I levels in fetal skin and gastric tract were higher than in fetal serum. This indicates ^{125}I was sequestered in these tissues. GD20 maternal perchlorate levels were present at the highest level in the thyroid, followed by gastric contents and serum. A time dependent increased perchlorate ratio (>1.0) for thyroid:serum of GD20 dams was observed in both 0.1 and 1 mg/kg dose groups.

a. Percent inhibition of iodide uptake in the thyroid of PND10 dams for the period of 24 hours after dosing with 1 mg/kg perchlorate was 47 to 82%. ^{125}I levels of PND10 maternal gastric content, gastric tract and mammary gland were higher than ^{125}I levels of maternal serum, which shows sequestering of iodide in these tissues. ^{125}I levels in neonatal gastric contents, gastric tract and skin were higher than in serum. The highest perchlorate levels in PND10 dams were found in the thyroid followed by gastric contents, mammary gland, skin and serum. Male and female neonatal gastric contents showed the highest perchlorate levels. No perchlorate was detected in skin of male and female neonates.

4. For further information, please contact me by phone: (937) 255-5150 ext. 3176, fax: (937) 255-1474 or e-mail: kyung.yu@wpafb.af.mil.


for KYUNG O. YU, Ph.D.
Operational Toxicology Branch

Attachment: Tables 1-6

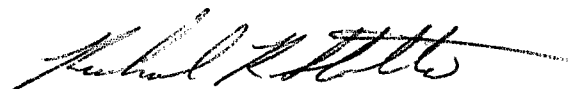
1st Ind, AFRL/HEST

7 January 2002

MEMORANDUM FOR US EPA

ATTN: MS. ANNIE JARABEK

This letter report has been coordinated at the branch level and is approved for release.

A handwritten signature in black ink, appearing to read "Richard R. Stotts", with a long horizontal flourish extending to the right.

RICHARD R. STOTTS, DVM, PhD
Branch Chief
Operational Toxicology Branch
Human Effectiveness Directorate

Table 1. ^{125}I concentrations in tissues of GD20 dams and fetuses dosed with carrier free ^{125}I (2.19 ng/kg) via tail vein injection

Time point (h)	Dam thyroid (ng/g)	Dam serum (pg/mL)	Dam gastric contents (pg/g)	Dam placenta (pg/g)	Dam mammary gland (pg/g)	Dam skin (pg/g)	Fetus serum (pg/mL)	Fetus gastric tract (pg/g)	Fetus skin (pg/g)
0.5	0.334 ± 0.146	3.694 ± 1.00	8.14 ± 3.36	3.57 ± 0.92	2.04 ± 0.73	2.57 ± 0.79	1.14 ± 0.724	1.18 ± 0.38	2.23 ± 0.95
2	0.904 ± 0.497	3.27 ± 0.913	6.90 ± 3.33	3.09 ± 0.72	2.67 ± 0.95	2.55 ± 0.69	1.322 ± 0.559	1.43 ± 0.82	2.35 ± 0.96
4	2.056 ± 0.768	2.520 ± 0.254	7.02 ± 3.13	2.91 ± 0.55	3.45 ± 1.05	2.25 ± 0.37	1.017 ± 0.582	1.95 ± 1.33	2.90 ± 1.25
8	2.708 ± 0.988	1.715 ± 0.294	3.22 ± 1.44	1.82 ± 0.52	3.26 ± 0.78	2.51 ± 2.08	0.756 ± 0.361	1.18 ± 0.74	2.85 ± 1.19

Data are mean ± standard deviation, n=6-9.

^{125}I represents total iodine (bound iodine plus free iodide).

Table 2. Perchlorate concentrations in tissues of GD20 dams (2A) and fetuses (2B) intravenously injected with perchlorate (0.1 mg/kg)

Table 2A.

Time point (h)	Dam thyroid ($\mu\text{g/g}$)	Dam serum ($\mu\text{g/mL}$)	Dam mammary gland ($\mu\text{g/g}$)	Dam placenta ($\mu\text{g/g}$)	Dam skin ($\mu\text{g/g}$)	Dam gastric contents ($\mu\text{g/g}$)
0.5	1.051 ± 0.110	0.144 ± 0.012	0.000 ± 0.000	0.031 ± 0.003	0.190 ± 0.015	0.531 ± 0.039
1	1.500 ± 0.134	0.139 ± 0.016	0.000 ± 0.000	0.101 ± 0.011	0.471 ± 0.037	1.388 ± 0.143
2	2.464 ± 0.162	0.159 ± 0.016	0.142 ± 0.009	0.112 ± 0.005	0.512 ± 0.035	0.489 ± 0.049
4	1.732 ± 0.189	0.150 ± 0.013	0.000 ± 0.000	0.076 ± 0.008	0.459 ± 0.028	0.000 ± 0.000
8	1.331 ± 0.151	0.061 ± 0.005	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
12	0.727 ± 0.077	0.043 ± 0.004	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
24	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
48	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000

Data are mean ± standard deviation, n=6.

Table 2B.

Time point (h)	Fetus serum ($\mu\text{g/mL}$)	Fetus skin ($\mu\text{g/g}$)	Fetus gastric tract ($\mu\text{g/g}$)
0.5	0.034 ± 0.002	0.000 ± 0.000	0.000 ± 0.000
1	0.037 ± 0.004	0.000 ± 0.000	0.000 ± 0.000
2	0.041 ± 0.002	0.184 ± 0.020	0.141 ± 0.014
4	0.049 ± 0.005	0.184 ± 0.016	0.000 ± 0.000
8	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
12	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
24	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
48	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000

Data are mean \pm standard deviation, n=6.

Table 3. Perchlorate concentrations in thyroid and serum of GD20 dam intravenously dosed with perchlorate (1 mg/kg)

Time point (h)	Thyroid ($\mu\text{g/g}$)	Serum ($\mu\text{g/mL}$)
2.5	5.937 ± 0.656	1.018 ± 0.069
3	5.932 ± 0.581	1.329 ± 0.148
4	3.975 ± 0.329	1.255 ± 0.104
6	3.818 ± 0.286	0.422 ± 0.035
10	3.797 ± 0.423	0.382 ± 0.027
14	3.159 ± 0.341	0.108 ± 0.010
26	1.150 ± 0.110	0.030 ± 0.003

Data are mean \pm standard deviation, n=6.

Table 4. $^{125}\text{I}^-$ concentrations in tissues of GD20 dams and fetuses dosed with carrier free iodide only (1.87 ng/kg) or carrier free $^{125}\text{I}^-$ 2 h post-dosing with 1 mg/kg perchlorate (both iv injections)

Time point (h)	Dam thyroid (ng/g)		Dam serum (pg/mL)		Fetus serum (pg/mL)	
	$^{125}\text{I}^-$ only	ClO_4^- with $^{125}\text{I}^-$	$^{125}\text{I}^-$ only	ClO_4^- with $^{125}\text{I}^-$	$^{125}\text{I}^-$ only	ClO_4^- with $^{125}\text{I}^-$
0.5	0.313 ± 0.136	0.098 ± 0.025	3.706 ± 0.353	4.186 ± 0.517	0.823 ± 0.247	0.652 ± 0.174
1	0.548 ± 0.185	0.067 ± 0.014	3.059 ± 0.412	3.960 ± 0.401	1.098 ± 0.372	0.872 ± 0.338
2	0.949 ± 0.184	0.125 ± 0.030	2.924 ± 0.486	3.542 ± 0.726	1.067 ± 0.209	0.980 ± 0.408
4	1.542 ± 0.617	0.278 ± 0.107	2.316 ± 0.334	2.773 ± 0.322	1.163 ± 0.625	0.950 ± 0.559
8	2.434 ± 0.471	0.662 ± 0.245	1.613 ± 0.274	1.655 ± 0.466	0.612 ± 0.097	0.766 ± 0.293
12	2.971 ± 0.655	0.563 ± 0.222	0.491 ± 0.126	0.444 ± 0.133	0.247 ± 0.065	0.167 ± 0.097
24	4.182 ± 1.573	1.382 ± 0.598	0.277 ± 0.079	0.191 ± 0.030	0.238 ± 0.136	0.150 ± 0.049

Data are mean \pm standard deviation, n=6.

$^{125}\text{I}^-$ represents total iodine (bound iodine plus free iodide).

Table 5. ^{125}I tissue concentrations in PND10 dams (5A) intravenously dosed with 2.1 ng/kg ^{125}I or ^{125}I 2 h post-dosing with 1 mg/kg perchlorate and ^{125}I tissue concentrations in PND10 neonates (5B) exposed via milk

Table 5A

Time point (h)	Dam thyroid (ng/g)		Dam serum (pg/mL)		Dam gastric contents (pg/g)		Dam gastric tract (pg/g)		Dam mammary gland (pg/g)		Dam skin (pg/g)	
	^{125}I only	ClO_4^- with ^{125}I	^{125}I only	ClO_4^- with ^{125}I	^{125}I only	ClO_4^- with ^{125}I	^{125}I only	ClO_4^- with ^{125}I	^{125}I only	ClO_4^- with ^{125}I	^{125}I only	ClO_4^- with ^{125}I
0.5	0.610 ± 0.084	0.108 ± 0.031	2.513 ± 0.427	3.315 ± 0.283	3.597 ± 1.526	3.658 ± 0.977	5.767 ± 0.560	2.484 ± 0.547	7.899 ± 1.944	5.104 ± 0.714	1.981 ± 0.549	2.454 ± 0.319
1	0.566 ± 0.166	0.161 ± 0.017	2.288 ± 0.461	2.937 ± 0.141	3.827 ± 0.644	4.180 ± 0.993	3.001 ± 1.098	2.438 ± 0.693	7.976 ± 3.346	5.637 ± 0.614	2.200 ± 0.631	2.645 ± 0.256
2	0.947 ± 0.457	0.317 ± 0.072	1.270 ± 0.597	2.228 ± 0.281	2.765 ± 1.217	3.907 ± 0.737	2.171 ± 1.204	1.814 ± 0.431	8.619 ± 3.777	7.059 ± 2.526	1.476 ± 0.221	1.829 ± 0.295
4	1.223 ± 0.298	0.435 ± 0.115	0.812 ± 0.369	1.365 ± 0.437	1.921 ± 0.912	2.175 ± 0.406	1.047 ± 0.630	1.367 ± 0.630	5.026 ± 1.651	5.476 ± 0.914	0.937 ± 0.316	1.286 ± 0.434
8	1.206 ± 0.382	0.608 ± 0.103	0.340 ± 0.062	0.320 ± 0.161	1.083 ± 0.699	0.779 ± 0.150	0.399 ± 0.122	0.399 ± 0.088	2.170 ± 0.785	2.587 ± 1.499	0.633 ± 0.375	0.638 ± 0.343
24	1.446 ± 0.599	0.765 ± 0.196	0.073 ± 0.016	0.078 ± 0.034	0.161 ± 0.040	0.172 ± 0.076	0.060 ± 0.015	0.067 ± 0.020	1.130 ± 2.164	0.368 ± 0.142	0.610 ± 0.547	0.531 ± 0.376

Data are mean ± standard deviation, n=6.

^{125}I represents as total iodine (bound iodine plus free iodide).

Table 5B

Time point (h)	Female neonate serum (ng/g)		Male neonate serum (pg/mL)		Neonate* gastric contents (pg/g)		Neonate* gastric tract (pg/g)		Neonate* skin (pg/g)	
	^{125}I only	ClO_4^- with ^{125}I	^{125}I only	ClO_4^- with ^{125}I	^{125}I only	ClO_4^- with ^{125}I	^{125}I only	ClO_4^- with ^{125}I	^{125}I only	ClO_4^- with ^{125}I
0.5	0.00503 \pm 0.01071	0.00426 \pm 0.00449	0.00393 \pm 0.00768	0.00352 \pm 0.00267	0.458 \pm 1.070	0.727 \pm 0.806	0.049 \pm 0.074	0.052 \pm 0.047	0.012 \pm 0.009	0.014 \pm 0.009
1	0.07277 \pm 0.03952	0.03214 \pm 0.01804	0.06569 \pm 0.03127	0.03160 \pm 0.02124	4.685 \pm 2.133	3.111 \pm 2.000	0.530 \pm 0.365	0.289 \pm 0.176	0.063 \pm 0.038	0.102 \pm 0.235
2	0.20672 \pm 0.10153	0.07325 \pm 0.05057	0.19148 \pm 0.09692	0.07360 \pm 0.04569	10.194 \pm 3.496	5.805 \pm 4.095	0.884 \pm 0.542	0.403 \pm 0.248	0.313 \pm 0.193	0.099 \pm 0.071
4	0.53596 \pm 0.08823	0.41061 \pm 0.10961	0.46591 \pm 0.07479	0.39263 \pm 0.13709	19.157 \pm 4.128	19.041 \pm 7.514	1.487 \pm 0.475	1.271 \pm 0.400	0.891 \pm 0.220	0.484 \pm 0.147
8	0.80752 \pm 0.16921	0.84500 \pm 0.19814	0.85458 \pm 0.20401	0.66883 \pm 0.23600	22.028 \pm 7.929	20.326 \pm 4.666	1.733 \pm 0.553	1.605 \pm 0.625	1.825 \pm 0.529	0.950 \pm 0.198
24	0.99285 \pm 0.14188	1.08023 \pm 0.40512	1.01391 \pm 0.19081	1.08915 \pm 0.37418	8.278 \pm 2.594	11.636 \pm 5.690	1.564 \pm 0.410	1.530 \pm 0.621	2.883 \pm 0.623	1.645 \pm 0.413

Data are mean \pm standard deviation, n=6; ^{125}I represents as total iodine (bound iodine plus free iodide).

*Combined ^{125}I levels of male and female neonates

Table 6. Perchlorate concentrations in tissues of PND10 dams iv dosed with 0.1 mg/kg perchlorate (6A) and in tissues of PND10 neonates exposed via milk (6B)

Table 6A

Time point (h)	Dam thyroid ($\mu\text{g/g}$)	Dam serum ($\mu\text{g/mL}$)	Dam mammary gland ($\mu\text{g/g}$)	Dam gastric contents ($\mu\text{g/g}$)	Dam skin ($\mu\text{g/g}$)
0.5	1.81 ± 0.18	0.083 ± 0.01	0.271 ± 0.04	0.453 ± 0.04	0.135 ± 0.01
1	1.54 ± 0.14	0.090 ± 0.01	0.479 ± 0.04	1.856 ± 0.17	0.201 ± 0.02
2	1.51 ± 0.15	0.144 ± 0.01	0.397 ± 0.04	0.369 ± 0.04	0.164 ± 0.02
4	0.74 ± 0.08	0.190 ± 0.02	0.176 ± 0.01	0.000 ± 0.00	0.118 ± 0.01
8	0.67 ± 0.06	0.000 ± 0.00	0.000 ± 0.00	0.000 ± 0.00	0.000 ± 0.00
12	0.00 ± 0.00	0.000 ± 0.00	0.000 ± 0.00	0.000 ± 0.00	0.000 ± 0.00

Data are mean \pm standard deviation, n=6.

Table 6B

Time point (h)	Female neonate serum ($\mu\text{g/mL}$)	Male neonate serum ($\mu\text{g/mL}$)	Female neonate gastric contents ($\mu\text{g/g}$)	Male neonate gastric contents ($\mu\text{g/g}$)	Female neonate skin ($\mu\text{g/g}$)	Male neonate skin ($\mu\text{g/g}$)
0.5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.00	0.000 ± 0.00	0.000 ± 0.000	0.000 ± 0.000
1	0.000 ± 0.000	0.000 ± 0.000	0.485 ± 0.05	0.828 ± 0.08	0.000 ± 0.000	0.000 ± 0.000
2	0.000 ± 0.000	0.000 ± 0.000	0.543 ± 0.06	0.308 ± 0.03	0.000 ± 0.000	0.000 ± 0.000
4	0.021 ± 0.002	0.025 ± 0.003	0.475 ± 0.05	0.282 ± 0.03	0.000 ± 0.000	0.000 ± 0.000
8	0.039 ± 0.003	0.034 ± 0.003	0.328 ± 0.04	0.274 ± 0.03	0.000 ± 0.000	0.000 ± 0.000
12	0.038 ± 0.002	0.038 ± 0.003	0.263 ± 0.03	0.265 ± 0.02	0.000 ± 0.000	0.000 ± 0.000

Data are mean \pm standard deviation, n=6.